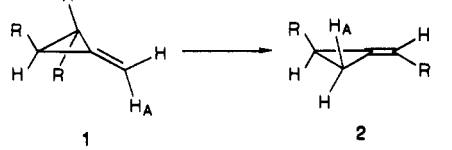
Stereoselectivity in the Methylenecyclopropane Rearrangement and Molecular Distortions in Methylenecyclopropane-2-carboxamide

Summary: An X-ray crystallographic structure determination for methylenecyclopropane-2-carboxamide reveals molecular distortions that correlate with known stereochemical preferences characteristic of the methylenecyclopropane rearrangement.

Sir: The stereochemical proclivities of the methylenecyclopropane rearrangement[1-3] remain imperfectly defined experimentally and ambiguously interpreted theoretically, in spite of substantial painstaking effort.[4] Kinetically competitive reactions that tend to obscure stereochemical correspondences between a substrate and a directly related [1,3] sigmatropic shift product,[5,6] system-dependent stereochemical findings,[8] and even disparate experimental results for identical methylenecyclopropanes,[3,7,8] impede efforts to arrive at generally valid rationalizations.

Yet several stereochemical aspects of the rearrangement seem to be well-defined. The generally preferred stereochemistry for the [1,3] sigmatropic carbon shift involves inversion at the pivot carbon[7] and suprafacial utilization of the allyl moiety;[9,10] experimental precedent often allows reliable prediction as to which endocyclic methylene unit will migrate preferentially and which will serve as the pivot carbon;[11] and substituents disposed trans at C2 and C3 are preferentially located anti in the kinetically controlled product mixture (1 → 2).[3,7,8,10,12] The last noted stereochemical feature may not be explained through invocation of simple arguments based on minimization of repulsive steric interactions for it persists even when the migration origin is deuteriomethylene[10] (3 ⇄ 4).



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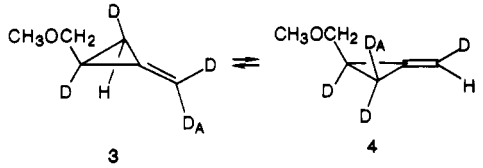

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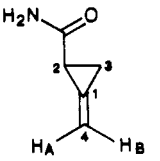
In an initial effort to learn whether the structural factors manifested in these stereochemical preferences during thermal rearrangement might be evident as well in a ground-state methylenecyclopropane, we have determined the structure of methylenecyclopropane-2-carboxamide (**5**)[13] by X-ray crystallography. This compound was selected for it is nicely crystalline and yet has a minimum number of heavy atoms, thus improving prospects for locating hydrogens with reasonable accuracy.



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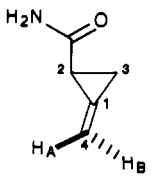
Racemic amide **5** was recrystallized from ethyl acetate; a crystal was mounted and data were collected at 23 °C as detailed in the supplementary material. It proved to be monoclinic, with space group $P2_1/c$ and eight molecules (two symmetry independent molecules) of C_5H_7NO in the unit cell; the cell constants are a = 7.4192, b = 15.941, and c = 9.097 Å and β = 104.20°. From a total of 1843 reflections collected, 1559 were accepted at statistically above background. In the refinement, described in the supplementary material, 183 parameters were varied. The full-matrix least-squares refinement converged at R = 0.051 and R_w = 0.068.

Both independent molecules in the unit cell have the planar amide function perpendicular to the three-membered ring, with oxygen and HC2 in a trans relationship, and *both exhibit significant distortions from an idealized geometry in a manner consonant with the stereochemical preferences shown by methylenecyclopropane rearrangements.*

The C2–C1–C4 and C3–C1–C4 angles in the two molecules are 145.5° (145.4°) and 150.9° (150.3°). Thus the exocyclic carbon is displaced from the plane perpendicular to the ring and bisecting the C2–C1–C3 angle so as to be closer to C2, the ring carbon substituted with the more stereochemically demanding amide function, and the preferred pivot atom in the methylenecyclopropane rearrangement.

While the X-ray crystallographic definitions of coordinates for the hydrogen atoms are less precise than are those for C, N, and O atoms, they are nevertheless indicative of a further sort of distortion of the core methylenecyclopropane skeleton from an idealized C_{2v} geometry. The exocyclic CH_2 groups in the two molecules do not share a common plane with the three-membered ring. The dihedral angles between planes defined by C1–C2–C3 and HA–C4–HB in the two crystallographically independent molecules are calculated to be 4.55° and 11.43°: the sense of distortion tilts HA toward the amide function. Both kinds of distortion—both displacement of C4 toward C2 and rotation of the HA–C4–HB plane with respect to the



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C1–C2–C3 plane, as summarized in the exaggerated depiction 6—have been confirmed through a complete neutron diffraction structure determination for this monosubstituted methylenecyclopropane.[14] Such corroborative evidence is especially important as verification of the second distortion, for neutron diffraction is a physical method much better suited to accurate location of hydrogen atoms in organic crystal structure determinations than X-ray crystallography.

These geometrical distortions, derived from "orbital distortions" associated with σ–π mixing,[15] reflect the sense of stereochemical bias shown consistently by methylenecyclopropane rearrangements, as in the example 3 ⇄ 4. That C2 is the favored pivot atom is mirrored in the displacement of C4 toward C2. Which diastereotopic face of the C4 methylene unit will preferentially bond with C2 as the methylenecyclopropane rearrangement occurs, and thus the favored transposition of the trans-C3 substituent to the anti-C4 location as the suprafacial [1,3] shift takes place, is apparent in the dihedral angles between C2–C1–C3 and HA–C4–HB in the ground state.

Recent experimental[16] and theoretical[17] efforts have made it abundantly clear that "orbital distortion" may influence the ground-state geometry of an addend in a manner indicative of stereoselectivity in cycloaddition reactions. The present finding suggests that similar correlations between ground-state geometry and reaction stereochemistry may be found in and may provide useful insights relevant to sigmatropic rearrangements and other unimolecular thermal reactions.

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Supplementary Material Available: Experimental and data deduction details, tables of coordinates, bond lengths, and bond angles, and an ORTEP drawing for the X-ray structure determination of **5** (5 pages). Ordering information is given on any current masthead page.

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A Brief, Convergent, Regioselective Synthesis of Naphthoquinones. A Formal Synthesis of Nanaomycin A and Deoxyfrenolicin

Summary: A new synthetic route to naphthoquinones, which involves the thermal rearrangement of alkynyl-substituted benzocyclobutenones, is reported.

Sir: Reported here are convergent, regioselective syntheses of the naphthoquinones **1a** and **1b**, compounds which have been employed as key synthetic precursors to the biologically important quinones nanaomycin A (**2a**) and deoxyfrenolicin (**2b**).[1-3] In this regard, new chemistry is also presented in the form of a potentially general naphthoquinone synthesis which was employed as the key step in the construction of **1a,b**.

Recent results reported from our laboratory concerning the thermal rearrangement of 4-alkynylcyclobutenones to quinones suggested the retrosynthetic approach to **1a**, as depicted in Scheme I.[4,5] Specifically, it was found that alkynylation of dione **4** with the lithium salt of benzylethyne gave a 9:1 mixture of the regioisomeric benzocyclobutanones. Significantly, the major product was observed to rearrange cleanly to 2-benzyl-8-methoxy-1,4-naphthoquinone upon thermolysis in refluxing *p*-xylene.[5] Thus, an entry to the naphthoquinone nucleus was established. Still another model study was accomplished which determined that allyl ethers of 4-alkynylcyclobutenols undergo ring expansion with allyl group migration upon thermolysis in refluxing *p*-xylene (138 °C).[5]

These studies encouraged investigations directed toward the preparation and thermolysis of methoxybenzocyclobutenones such as **3**. Results from Liebeskind's laboratory as well as our own experience suggested that monoalkynylation of **4** might result in a mixture of regioisomers due to incomplete selection for alkynylation at the more electron-deficient carbonyl.[6] This proved to be true as evidenced by the fact that alkynylation of dione **4** with the lithium salt of 3-(tetrahydropyranyloxy)propyne (2:1 mixture of diastereomers) at −78 °C in THF gave **5a** (yellow oil) and its regioisomer in 85% yield in a respective ratio of 3:1; furthermore each regioisomer was formed as a 2:1 mixture of diastereomers (Scheme II).[7] Upon further experiment with **4** and other lithium acetylides it was found that regioselectivities of >95:5 were obtained at −100 °C in a mixed solvent of THF/diethyl ether (1:1).[8]

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